Complete Summary

GUIDELINE TITLE

The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003 Nov 25;61(10):1332-8. [48 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Multiple sclerosis (MS)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Neurology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To consider both the evidence leading to the recent Food and Drug Administration (FDA) approval as well as the appropriate clinical role of mitoxantrone (Novantrone) in the management of patients with multiple sclerosis

TARGET POPULATION

Patients with multiple sclerosis (MS) including secondary progressive MS (SPMS), progressive-relapsing MS, and worsening relapsing-remitting (RR) MS.

INTERVENTIONS AND PRACTICES CONSIDERED

Mitoxantrone (Novantrone) for treatment of multiple sclerosis

MAJOR OUTCOMES CONSIDERED

- Effect on disease progression
- Clinical attack rate
- Magnetic resonance imaging (MRI) outcomes
- Median time to first relapse

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Articles for this review were searched in Medline under the keywords mitoxantrone and multiple sclerosis (MS). Forty-one articles were identified by this search. The abstracts of these articles were reviewed and the original articles were selected for inclusion in the analysis only if they were either controlled trials or case series using mitoxantrone in the treatment of MS. Five such articles were identified, in addition to the phase III trial. In addition, the reference lists of the articles found in this manner were also reviewed to identify articles or abstracts not found by the computer search.

NUMBER OF SOURCE DOCUMENTS

- Forty-one articles were identified by the electronic search.
- The abstracts of these articles were reviewed and the original articles were selected for inclusion in the analysis only if they were either controlled trials or case series using mitoxantrone in the treatment of MS. Five such articles were identified, in addition to the phase III trial.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Rating of therapeutic article

Class I: Prospective, randomized, controlled clinical trial (RCT) with masked outcome assessment, in a representative population. The following are required:

a. Primary outcome(s) is/are clearly defined.
b. Exclusion/inclusion criteria are clearly defined.
c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.
d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criterion a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When formulating the recommendations the guideline developers considered the magnitude of the effect (benefit or harm of therapy, accuracy of tests, yield of studies) and the relative value of various outcomes. Under most circumstances, there is a direct link between the level of evidence used to formulate conclusions

and the strength of the recommendation. This linkage is illustrated in Appendix 9 of the 2004 AAN Guideline Process Manual (see Companion Documents field). Thus, an "established as" (two class I) conclusion supports a "should be done" (level A) recommendation; a "probably effective" (two class II) conclusion supports a "should be considered" (level B) recommendation; a "possibly effective" (two class III) conclusion supports a "may be considered" recommendation. In those circumstances where the evidence indicates that the intervention is not effective or useful, wording was modified. For example, if multiple adequately powered class I studies demonstrated that an intervention is not effective, the recommendation read, "should not be done."

There are important exceptions to the rule of having a direct linkage between the level of evidence and the strength of recommendations. Some situations where it may be necessary to break this linkage are listed below:

- A statistically significant but marginally important benefit of the intervention is observed
- The intervention is exorbitantly costly
- Superior and established alternative interventions are available
- There are competing outcomes (both beneficial and harmful) that cannot be reconciled

Under such circumstances the guideline developers may have downgraded the level of the recommendation.

Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population.

B = Probably effective, ineffective, or harmful for the given condition in the specified population.

C = Possibly effective, ineffective, or harmful for the given condition in the specified population.

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

Translation of Evidence to Recommendations

Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating requires at least one convincing class II study or at least three consistent class III studies.

Level C rating requires at least two convincing and consistent class III studies.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The reviewer of early drafts of the manuscript is acknowledged in the original guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Practice Recommendations

1. On the basis of evidence from a single Class I study and a few Class II or III studies, it appears that mitoxantrone may have a beneficial effect on disease progression in patients with multiple sclerosis (MS) whose clinical condition is deteriorating (Type B recommendation). In general, however, this agent is of limited use and of potentially great toxicity. Therefore, it should be reserved for patients with rapidly advancing disease who have failed other therapies.
2. On the basis of several consistent Class II and III studies, mitoxantrone probably reduces the clinical attack rate and reduces attack-related magnetic resonance imaging (MRI) outcomes in patients with relapsing MS (Type B recommendation). The potential toxicity of mitoxantrone, however, considerably limits its use in patients with relapsing forms of MS.
3. Because of the potential toxicity of mitoxantrone, it should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapeutic agents (Type A Recommendation). In addition, patients being treated with mitoxantrone should be monitored routinely for cardiac, liver, and kidney function abnormalities (Type A Recommendation).

Definitions:

Rating of Recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population.

B = Probably effective, ineffective, or harmful for the given condition in the specified population.

C = Possibly effective, ineffective, or harmful for the given condition in the specified population.

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

Translation of Evidence to Recommendations

Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating requires at least one convincing class II study or at least three consistent class III studies.

Level C rating requires at least two convincing and consistent class III studies.

Rating of therapeutic article

Class I: Prospective, randomized, controlled clinical trial (RCT) with masked outcome assessment, in a representative population. The following are required:

a. Primary outcome(s) is/are clearly defined.
b. Exclusion/inclusion criteria are clearly defined.
c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.
d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criterion a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

There is evidence from several Class II and III studies that mitoxantrone reduces clinical attack rate and attack-related magnetic resonance imaging (MRI) outcome measures in patients with relapsing forms of multiple sclerosis (MS).

POTENTIAL HARMS

- Adverse effects of mitoxantrone
- Use of this agent in relapsing MS will have to take into account its potential toxicity. Patients treated with mitoxantrone are at increased risk for cardiac toxicity as manifested by cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure.
- Because of concerns about such potential cardiac toxicity, a cumulative dose of mitoxantrone more than 140 mg/m^2 is not recommended for treatment of MS, although doses of up to 96 mg/m^2 seem to be safe.
- Other potential side effects include amenorrhea, which in some cases can be permanent, and a risk of late malignancy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Because of the modest clinical benefits on disease progression reported in the pivotal phase III mitoxantrone trial, this result should be replicated in another (and hopefully much larger) clinical trial before mitoxantrone can be recommended widely for the treatment of patients with multiple sclerosis (MS).
- This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003 Nov 25;61(10):1332-8. [48 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Nov 25

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

American Academy of Neurology (AAN) Therapeutics and Technology Assessment Subcommittee Members: Douglas S. Goodin, MD (Chair); Yuen T. So (Vice-chair); Carmel Armon, MD, MHS; Richard M. Dubinsky, MD; Mark Hallett, MD; David

Hammond, MD; Cynthia L. Harden, MD; Chung Y. Hsu, MD, PhD; Andres M. Kanner, MD; David S. Lefkowitz, MD; Janis Miyasaki, MD; Michael A. Sloan, MD; James C. Stevens, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology (AAN). Available from the AAN Web site.
- Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p. Electronic copies available in Portable Document Format (PDF) from the AAN Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on August 17, 2004. The information was verified by the guideline developer on September 9, 2004.

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